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FOLEY & LARDNER LLP 1530 PAGE MILL ROAD PALO ALTO, CA 94304			CROW, ROBERT THOMAS	
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			1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/678,760	Applicant(s) HEEGER ET AL.	
	Examiner Robert T. Crow	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 5 April 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-56 is/are pending in the application.
- 4a) Of the above claim(s) 53-56 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-52 is/are rejected.
- 7) ☒ Claim(s) 36 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 03 October 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner. .
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) ☒ Notice of References Cited (PTO-892) | 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) ☐ Notice of Informal Patent Application (PTO-152) |
| 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) ☐ Other: _____ |

SUPPLEMENTAL OFFICE ACTION

1. The previous Office Action, mailed 7 August 2006, is withdrawn.
2. This Supplemental Office Action is being provided with the following:
 - A. An objection to claim 36.
 - B. Correct of typographical errors in the rejection of claim 4.
 - C. New art rejections of claims 36-42 and 44 under 35 USC 102(b).
 - D. New art rejections of claim 43 and 45-52 under 35 USC 103(a).
 - E. Non-statutory double patenting rejections as outlined below.
3. The remaining text of the Office Action is unchanged.
4. This is a complete Office Action intended to replace the Office Action mailed 7 August 2006.

Election/Restrictions

Applicant's election of Group I in the reply filed on 5 April 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 53-56 are withdrawn. Claims 1-52 are currently under prosecution.

Information Disclosure Statement

The Information Disclosure Statement filed 5 April 2006 is acknowledged. However, only the Abstracts of documents CN 1422960 and CN 1422961 are being considered because English translations of the remainder of the documents have not been provided.

Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosure.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this

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application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice to Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Specifically, the Specification discloses nucleotide sequences in paragraphs 0073 and 0085. However, the sequences do not have SEQ ID NOS. In addition, a paper or compact disc copy of a "Sequence Listing" has not been provided, nor has a computer readable form (CRF) containing the "Sequence Listing" has been provided. Finally, a statement that the "Sequence Listing" content of the paper or compact disc "Sequence Listing" is the same as the content of the computer readable copy.

For compliance with sequence rules, it is necessary to include all sequences in the "Sequence Listing" and identify them with SEQ ID NO. In general, any sequence that is disclosed and/or claimed as a string of particular bases or amino acids, and that otherwise meets the criteria of CFR 1.821(a), must be set forth in the "Sequence Listing." See MPEP 2422.03.

While the Examiner has made every attempt to check the Specification for sequence compliance, Applicant is required to carefully check the entire Specification for any and all issues regarding sequence compliance.

For the response to this Office Action to be complete, Applicant is REQUIRED to comply with the Requirements for Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Failure to comply with the Requirements will be considered nonresponsive.

Specification

The disclosure is objected to because of the following informalities: the nucleotide sequences in paragraphs 0073 and 0085 do not have SEQ ID NOS.

Appropriate correction is required.

Claim Objections

Claim 36 is objected to because of the following informalities: claim 36 recites the limitation "proximity" in lines 13 and 19 of the claim. This appears to be a typographical error. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5, 10-15, 17, 19, 21, 24, 25, 28, and 30-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claims 5, 10, 15, 24, and 25 are indefinite in claim 5, which recited the limitation "claims 1-4" in line 1 of claim 5. The dependency of the claim is unclear.

2. Claims 11-15, 17, 19, 21, 25, 28, and 30 are indefinite in claims 11-15, which recite the limitation "the result" in line 2 of each of claims 11-15. There is insufficient antecedent basis for this limitation in each of the claims. It is suggested that the word "the" be changed to "a" in each of the claims. Claims 11-15, 17, 19, 21, 14, 25, 28, and 30 are also indefinite in claims 11-15, which recite the limitation "the polynucleotide" at the end of each of claims 11-15. It is unclear if "the polynucleotide" refers to the immobilized polynucleotide probe or if "the polynucleotide" refers to the polynucleotide target.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 4-7, 9-12, 14-19, 22-25, 33, 35-42, and 44 rejected under 35 U.S.C. 102(b) as being anticipated by Lee et al (PCT Publication No. WO 01/40511 A2, published 7 June 2001).

Regarding claim 1, Lee et al teach a detector for determining the presence of a target polynucleotide having a target nucleotide sequence (Abstract) comprising:

an electrode capable of sensing redox events in a redox moiety (e.g., electrodes in a microreaction vessel; page 19, line 36-page 20, line 8), and

an immobilized probe (e.g., a probe immobilized on an electrode; page 4, line 35-page 14, line 2), the probe carrying a redox moiety (page 12, lines 5-9) and having a probe nucleotide sequence which hybridizes with the target nucleotide sequence (page 12, lines 5-9) and

having a first configuration in the absence of hybridization with the target polynucleotide, which located the redox moiety in a first position relative to the electrode and having a second configuration, in the presence of hybridization with the target polynucleotide, which locates the redox moiety in a second position relative to the electrode (e.g., the probe is a molecular beacon, which forms a hairpin in the absence of a complementary sequence, wherein after hybridization, a pair of labels are separated; page 3, lines 24-31),

said first and second positions giving rise to distinguishable redox events detectable by the electrodes (e.g., hybridization results in a change in the redox properties of a pair of labels that are recorded electrochemically; page 12, lines 5-9).

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Regarding claim 2, Lee et al teach the detector of claim 1 wherein the first position is closer to the electrode is that the second position (e.g., the probe is a molecular beacon, which forms a hairpin in the absence of a complementary sequence, wherein after hybridization to a target, a pair of labels are separated [page 3, lines 24-31], wherein the redox moiety of claim 1 is the label within the pair of labels that is further away from the electrode after hybridization).

Regarding claim 4, Lee et al teach the detector of claim 1 wherein the probe is immobilized on the on the electrode at a position distant from the redox moiety (e.g., the redox moiety is the label within the pair of labels that is the furthest from the electrode; page 3, lines 24-31).

Regarding claim 5, Lee et al teach the detector of claim 1 wherein the electrode is capable of inducing redox events in the redox moiety (e.g., application of an electrochemical potential is applied to induce hybridization [page 17, lines 19-32], wherein the hybridization results in a change in the redox properties of a pair of labels that are recorded electrochemically; page 12, lines 5-9).

Regarding claim 6, Lee et al teach the detector of claim 1 wherein the first configuration comprises internal hybridization between two regions in the polynucleotide probe (e.g., the probe is a molecular beacon, which forms a hairpin in the absence of a complementary sequence; page 3, lines 24-31).

Regarding claim 7, Lee et al teach the detector of claim 2 wherein the first configuration comprises internal hybridization between two regions in the polynucleotide probe (e.g., the probe is a molecular beacon, which forms a hairpin in the absence of a complementary sequence; page 3, lines 24-31).

Regarding claim 9, Lee et al teach the detector of claim 4 wherein the first configuration comprises internal hybridization between two regions in the polynucleotide probe (e.g., the probe is a molecular beacon, which forms a hairpin in the absence of a complementary sequence; page 3, lines 24-31).

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Regarding claim 10, Lee et al teach the detector of claim 5 wherein the first configuration comprises internal hybridization between two regions in the polynucleotide probe (e.g., the probe is a molecular beacon, which forms a hairpin in the absence of a complementary sequence; page 3, lines 24-31).

Regarding claim 11, Lee et al teach the detector of claim 6 wherein the second configuration comprises a disrupted internal hybridization as the result of hybridization between a region in the polynucleotide probe and a complementary region in the polynucleotide (e.g., the probe is a molecular beacon, which forms a hairpin in the absence of a complementary sequence, wherein after hybridization, a pair of labels are separated; page 3, lines 24-31).

Regarding claim 12, Lee et al teach the detector of claim 7 wherein the second configuration comprises a disrupted internal hybridization as the result of hybridization between a region in the polynucleotide probe and a complementary region in the polynucleotide (e.g., the probe is a molecular beacon, which forms a hairpin in the absence of a complementary sequence, wherein after hybridization, a pair of labels are separated; page 3, lines 24-31).

Regarding claim 14, Lee et al teach the detector of claim 9 wherein the second configuration comprises a disrupted internal hybridization as the result of hybridization between a region in the polynucleotide probe and a complementary region in the polynucleotide (e.g., the probe is a molecular beacon, which forms a hairpin in the absence of a complementary sequence, wherein after hybridization, a pair of labels are separated; page 3, lines 24-31).

Regarding claim 15, Lee et al teach the detector of claim 10 wherein the second configuration comprises a disrupted internal hybridization as the result of hybridization between a region in the polynucleotide probe and a complementary region in the polynucleotide (e.g., the probe is a molecular beacon, which forms a hairpin in the absence of a complementary sequence, wherein after hybridization, a pair of labels are separated; page 3, lines 24-31).

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Regarding claim 16, Lee et al teach the detector of claim 6, wherein the polynucleotide probe in its first configuration is a stem and hairpin configuration (page 3, lines 24-31) with the stem immobilized on the electrode and with the redox moiety attached to the end of the polynucleotide distal to the stem (e.g., the redox moiety is the label within the pair of labels that is on the furthest from the electrode; page 3, lines 24-31).

Regarding claim 17, Lee et al teach the detector of claim 11, wherein the polynucleotide probe in its first configuration is a stem and hairpin configuration (page 3, lines 24-31) with the stem immobilized on the electrode and with the redox moiety attached to the end of the polynucleotide distal to the stem (e.g., the redox moiety is the label within the pair of labels that is on the furthest from the electrode; page 3, lines 24-31).

Regarding claim 18, Lee et al teach the detector of claim 7, wherein the polynucleotide probe in its first configuration is a stem and hairpin configuration (page 3, lines 24-31) with the stem immobilized on the electrode and with the redox moiety attached to the end of the polynucleotide distal to the stem (e.g., the redox moiety is the label within the pair of labels that is on the furthest from the electrode; page 3, lines 24-31).

Regarding claim 19, Lee et al teach the detector of claim 2, wherein the polynucleotide probe in its first configuration is a stem and hairpin configuration (page 3, lines 24-31) with the stem immobilized on the electrode and with the redox moiety attached to the end of the polynucleotide distal to the stem (e.g., the redox moiety is the label within the pair of labels that is on the furthest from the electrode; page 3, lines 24-31).

Regarding claim 22, Lee et al teach the detector of claim 9, wherein the polynucleotide probe in its first configuration is a stem and hairpin configuration (page 3, lines 24-31) with the stem immobilized on the electrode and with the redox moiety attached to the end of the polynucleotide distal to the stem (e.g., the redox moiety is the label within the pair of labels that is on the furthest from the electrode; page 3, lines 24-31).

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Regarding claim 23, Lee et al teach the detector of claim 14, wherein the polynucleotide probe in its first configuration is a stem and hairpin configuration (page 3, lines 24-31) with the stem immobilized on the electrode and with the redox moiety attached to the end of the polynucleotide distal to the stem (e.g., the redox moiety is the label within the pair of labels that is on the furthest from the electrode; page 3, lines 24-31).

Regarding claim 24, Lee et al teach the detector of claim 10, wherein the polynucleotide probe in its first configuration is a stem and hairpin configuration (page 3, lines 24-31) with the stem immobilized on the electrode and with the redox moiety attached to the end of the polynucleotide distal to the stem (e.g., the redox moiety is the label within the pair of labels that is on the furthest from the electrode; page 3, lines 24-31).

Regarding claim 25, Lee et al teach the detector of claim 15, wherein the polynucleotide probe in its first configuration is a stem and hairpin configuration (page 3, lines 24-31) with the stem immobilized on the electrode and with the redox moiety attached to the end of the polynucleotide distal to the stem (e.g., the redox moiety is the label within the pair of labels that is on the furthest from the electrode; page 3, lines 24-31).

Regarding claim 33, Lee et al teach the detector of claim 1 wherein the electrode comprises a metal (page 8, lines 15-21).

Regarding claim 35, Lee et al teach the detector of claim 1 wherein the redox moiety is ethidium bromide (page 15, lines 5-15).

Regarding claim 36, Lee et al teach a detector for determining the presence of a target polynucleotide having a target nucleotide sequence (Abstract), said detector comprising an electrode capable of sensing redox events in a redox moiety (e.g., electrodes in a microreaction vessel; page 19, line 36-page 20, line 8), and an immobilized probe (e.g., a probe immobilized on an electrode; page 4, line 35-page 14, line 2), the probe carrying a redox moiety (page 12, lines 5-9) and having a probe nucleotide sequence which hybridizes with the target nucleotide sequence (page 12, lines 5-9).

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Lee et al teach also probes comprising hairpin loops (e.g., molecular beacons; page 3, lines 24-31), and hybridization to the target resulting in a change in the redox properties of a pair of labels that are recorded electrochemically (page 12, lines 5-9). The second and fourth regions of the instant claims are interpreted to be the half of the hybridized stem portion of the hairpin loop of Lee et al that is closest to the electrode when the hairpin loop is formed. The third region of hairpin forming length of the instant claim is interpreted to be the half of the hybridized stem portion of the hairpin loop of Lee et al that is the furthest from the electrode. The instantly claimed first portion is the end of the probe immobilized on the electrode, and the instantly claimed fifth portion is the other end of the probe.

Lee also teaches that the redox moiety is in proximity to the electrode when the second and fourth regions are hybridized, and that when a target hybridizes to at least a portion of the second, third, and fourth regions of the probe, the hybridization interferes with the redox moiety being in proximity to the electrode (e.g., the probe is a molecular beacon, which forms a hairpin in the absence of a complementary sequence, wherein after hybridization, a pair of labels are separated; page 3, lines 24-31).

Regarding claim 37, Lee et al teach the detector of claim 36 additionally comprising means for detecting electron transduction between the electrode and the redox moiety when the hairpin (e.g., the hybridization results in a change in the redox properties of a pair of labels that are recorded electrochemically; page 12, lines 5-9).

Regarding claim 38, Lee et al teach the detector of claim 37 additionally comprising means for inducing electron transduction between the electrode and the redox moiety when the hairpin is formed (e.g., application of an electrochemical potential is applied to induce hybridization; page 17, lines 19-32).

Regarding claim 39, Lee et al teach the detector of claim 38 wherein the first region is at one end of the probe (e.g., one end is immobilized to the electrode; page 4, line 35-page 14, line 2).

Regarding claims 40 and 41, Lee et al teach the detector of claim 38 wherein the fifth region is at one end of the probe, wherein the end is the second end (e.g., Figure 12).

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Regarding claim 42, Lee et al teach the detector of claim 36 wherein electrode comprises a metal (page 8, lines 15-21).

Regarding claim 44, Lee et al teach the detector of claim 36 wherein the redox moiety is ethidium bromide (page 15, lines 5-15).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

1. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

2. Claims 1, 3, 8, 13, 20, and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (PCT Publication No. WO 01/40511 A2, published 7 June 2001) in view of Fan et al (U.S. Patent Application Publication No. US 2002/0006617 A1, published 17 January 2002).

Regarding claim 3, Lee et al teach a detector for determining the presence of a target polynucleotide of claim 1 having a target nucleotide sequence (Abstract) comprising an electrode capable of sensing redox events in a redox moiety (e.g., electrodes in a microreaction vessel; page 19, line 36-page

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20, line 8), and an immobilized probe (e.g., a probe immobilized on an electrode; page 4, line 35-page 14, line 2), the probe carrying a redox moiety (page 12, lines 5-9) and having a probe nucleotide sequence which hybridizes with the target nucleotide sequence (page 12, lines 5-9) and having a first configuration in the absence of hybridization with the target polynucleotide, which located the redox moiety in a first position relative to the electrode and having a second configuration, in the presence of hybridization with the target polynucleotide, which locates the redox moiety in a second position relative to the electrode (e.g., the probe is a molecular beacon, which forms a hairpin in the absence of a complementary sequence, wherein after hybridization, a pair of labels are separated; page 3, lines 24-31), said first and second positions giving rise to distinguishable redox events detectable by the electrodes (e.g., hybridization results in a change in the redox properties of a pair of labels that are recorded electrochemically; page 12, lines 5-9). Lee et al are silent with respect to the second position having the second position closer to the electrode.

However, Fan et al teach immobilized target nucleic acids (paragraph 0078) and rolling circle probes that bind the target nucleic acid (paragraph 0094, wherein the hybridization immobilizes the probe) wherein the probe has a label sequence (number 150 of Figure 10 and paragraph 0014), wherein upon hybridization the label moves closer to the surface (i.e., the rolling circle probe hybridizes one end first, thereby becoming immobilized, followed by hybridization of the second end, which brings the label sequence closer to the surface by locking it in open circle form) with the added advantage that rolling circle probes allow polymerase to extend the probe repeatedly (paragraph 0091).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the detector as taught by Lee et al with the probes as taught by Fan et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in repeated extension of the probe as explicitly taught by Fan et al (paragraph 0091).

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Regarding claim 8, the detector of claim 3 is discussed above. Lee et al teach also the detector wherein the first configuration comprises internal hybridization between two regions in the polynucleotide probe (e.g., the probe is a molecular beacon, which forms a hairpin in the absence of a complementary sequence; page 3, lines 24-31).

Regarding claim 13, the detector of claim 8 is discussed above. Lee et al teach the detector wherein the second configuration comprises a disrupted internal hybridization as the result of hybridization between a region in the polynucleotide probe and a complementary region in the polynucleotide (e.g., the probe is a molecular beacon, which forms a hairpin in the absence of a complementary sequence, wherein after hybridization, a pair of labels are separated; page 3, lines 24-31).

Regarding claim 20, the detector of claim 8 is discussed above. Lee et al also teach the polynucleotide probe in its first configuration is a stem and hairpin configuration (page 3, lines 24-31) with the stem immobilized on the electrode and with the redox moiety attached to the end of the polynucleotide distal to the stem (e.g., the redox moiety is the label within the pair of labels that is on the furthest from the electrode; page 3, lines 24-31).

Regarding claim 21, the detector of claim 13 is discussed above. Lee et al also teach the polynucleotide probe in its first configuration is a stem and hairpin configuration (page 3, lines 24-31) with the stem immobilized on the electrode and with the redox moiety attached to the end of the polynucleotide distal to the stem (e.g., the redox moiety is the label within the pair of labels that is on the furthest from the electrode; page 3, lines 24-31).

3. Claims 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (PCT Publication No. WO 01/40511 A2, published 7 June 2001) as applied to claims 1, 6, and 11 above, and in view of Egholm et al (U.S. Patent No. 6,451,588 B1, issued 17 September 2002).

Regarding claims 26-27, the detectors of claims 1, 6, and 11 are discussed above. Lee et al are silent with respect to internal hybridization in the second conformation.

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However, Egholm et al teach immobilized nucleic acid probes (column 15, lines 40-53) wherein upon hybridization to the target, the probe comprises internal hybridization (e.g., Figures 4C and 4D, where the probe is a pair of probes [Figure 4C] that, upon hybridization to target 20, has a hybridization region maintained between probes 44 and 46; column 12, lines 1-13) with the added advantage of allowing use of two low-complexity libraries having less than 0.005% of the probes required by a single high-complexity library (column 14, lines 24-47).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the detector as taught by Lee et al with the probes as taught by Egholm et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in allowing use of two low-complexity libraries having less than 0.005% of the probes required by a single high-complexity library as explicitly taught by Egholm et al (column 14, lines 24-47).

4. Claims 29-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (PCT Publication No. WO 01/40511 A2, published 7 June 2001) and Fan et al (U.S. Patent Application Publication No. US 2002/0006617 A1, published 17 January 2002) as applied to claims 1, 3, 8, and 13 above, and in view of Egholm et al (U.S. Patent No. 6,451,588 B1, issued 17 September 2002).

Regarding claims 29-30, the detectors of claims 1, 3, 8, and 13 are discussed above. Lee et al and Fan et al are silent with respect to internal hybridization in the second conformation.

However, Egholm et al teach immobilized nucleic acid probes (column 15, lines 40-53) wherein upon hybridization to the target, the probe comprises internal hybridization (e.g., Figures 4C and 4D, where the probe is a pair of probes [Figure 4C] that, upon hybridization to target 20, has a hybridization region maintained between probes 44 and 46; column 12, lines 1-13) with the added advantage of allowing use of two low-complexity libraries having less than 0.005% of the probes required by a single high-complexity library (column 14, lines 24-47).

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It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the detector as taught by Lee et al and Fan et al with the probes as taught by Egholm et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in allowing use of two low-complexity libraries having less than 0.005% of the probes required by a single high-complexity library as explicitly taught by Egholm et al (column 14, lines 24-47).

5. Claims 31 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (PCT Publication No. WO 01/40511 A2, published 7 June 2001) and Fan et al (U.S. Patent Application Publication No. US 2002/0006617 A1, published 17 January 2002) as applied to claims 1 and 3 above, and further in view of Rothberg et al (U.S. Patent Application Publication No. US 2002/0012930 A1, published 31 January 2002).

Regarding claims 31 and 32, the detectors of claims 1 and 3 are discussed above. While Fan et al teach rolling circle probes (paragraph 0094), neither Lee et al nor Fan et al teach loops in the target in the second conformation.

However, Rothberg et al teach rolling circle probes having a loop in the target (e.g., Figure 1D, wherein the hybridized circular molecule leaves a loop [i.e., the gap in Figure 1D] in the immobilized target) with the added advantage that the rolling circle probes allow isothermal amplification of thousands of copies of the nucleic acid (paragraph 0087).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the detector as taught by Lee et al and Fan et al with the probes as taught by Rothberg et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in allowing isothermal amplification of thousands of copies of the nucleic acid as explicitly taught by Rothberg et al (paragraph 0087).

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6. Claims 33-34, 36, 42, 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (PCT Publication No. WO 01/40511 A2, published 7 June 2001) as applied to claim 1 above, and further in view of Hashimoto (U.S. Patent Application Publication No. US 2001/0024788 A1, issued 27 September 2001).

Regarding claim 34, the detector of claim 1 is discussed above. While Lee et al also teach the detector of claim 33 wherein the electrode comprises a metal (page 8, lines 15-21), Lee et al are silent with respect to gold.

However, Hashimoto teaches a nucleic acid carrier for electric detection of nucleic acids (Abstract) comprising gold electrodes and immobilized thiolated nucleic acids with the added advantage that gold is preferable for immobilizing sulfur-bearing nucleic acids because of the high affinity of gold for sulfur (paragraph 0032).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the detector as taught by Lee et al with the gold electrodes as taught by Hashimoto with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in high affinity immobilization of nucleic acids to the electrodes as explicitly taught by Hashimoto (paragraph 0032).

Regarding claim 43, Lee et al teach the detector of claim 36 for determining the presence of a target polynucleotide having a target nucleotide sequence (Abstract), said detector comprising an electrode capable of sensing redox events in a redox moiety (e.g., electrodes in a microreaction vessel; page 19, line 36-page 20, line 8), and an immobilized probe (e.g., a probe immobilized on an electrode; page 4, line 35-page 14, line 2), the probe carrying a redox moiety (page 12, lines 5-9) and having a probe nucleotide sequence which hybridizes with the target nucleotide sequence (page 12, lines 5-9).

Lee et al teach also probes comprising hairpin loops (e.g., molecular beacons; page 3, lines 24-31), and hybridization to the target resulting in a change in the redox properties of a pair of labels that are

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recorded electrochemically (page 12, lines 5-9). The second and fourth regions of the instant claims are interpreted to be the half of the hybridized stem portion of the hairpin loop of Lee et al that is closest to the electrode when the hairpin loop is formed. The third region of hairpin forming length of the instant claim is interpreted to be the half of the hybridized stem portion of the hairpin loop of Lee et al that is the furthest from the electrode. The instantly claimed first portion is the end of the probe immobilized on the electrode, and the instantly claimed fifth portion is the other end of the probe.

Lee also teaches that the redox moiety is in proximity to the electrode when the second and fourth regions are hybridized, and that when a target hybridizes to at least a portion of the second, third, and fourth regions of the probe, the hybridization interferes with the redox moiety being in proximity to the electrode (e.g., the probe is a molecular beacon, which forms a hairpin in the absence of a complementary sequence, wherein after hybridization, a pair of labels are separated; page 3, lines 24-31).

Lee et al teach also the detector of claim 42, wherein electrode comprises a metal (page 8, lines 15-21).

Lee et al are silent with respect to gold.

However, Hashimoto teaches a nucleic acid carrier for electric detection of nucleic acids (Abstract) comprising gold electrodes and immobilized thiolated nucleic acids with the added advantage that gold is preferable for immobilizing sulfur-bearing nucleic acids because of the high affinity of gold for sulfur (paragraph 0032).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the detector as taught by Lee et al with the gold electrodes as taught by Hashimoto with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in high affinity immobilization of nucleic acids to the electrodes as explicitly taught by Hashimoto (paragraph 0032).

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7. Claims 45-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (PCT Publication No. WO 01/40511 A2, published 7 June 2001) in view of Lizardi et al (U.S. Patent No. 5,312,728, issued 17 May 1994).

Regarding claim 45, Lee et al teach a detector for determining the presence of a target polynucleotide having a target nucleotide sequence (Abstract), said detector comprising:

an electrode capable of sensing redox events in a redox moiety (e.g., electrodes in a microreaction vessel; page 19, line 36-page 20, line 8), and polynucleotide probe (e.g., a probe immobilized on an electrode; page 4, line 35-page 14, line 2), the probe carrying a redox moiety (page 12, lines 5-9) and having a probe nucleotide sequence which hybridizes with the target nucleotide sequence (page 12, lines 5-9). While Lee et al teach probes comprising hairpins (e.g., molecular beacons; page 3, lines 24-31), and hybridization to the target resulting in a change in the redox properties of a pair of labels that are recorded electrochemically (page 12, lines 5-9), Lee et al do not teach first through third regions forming loops (i.e., probes that convert from one stem-loop to another).

However, Lizardi et al teach a probe nucleic acid that is a single molecule (e.g., column 14, Example V and Figure 12) having a first nucleotide sequence complementary to and spaced apart from a second nucleotide sequence with which it self hybridizes to form a first loop (e.g., elements 31-33 of Figure 12, including switch sequences 32 and 33; Example V), wherein upon binding to a target (element 8 of Figure 13), the first sequence binds to the target and the first loop is disrupted (i.e., loop 31 binds to the target [Figure 13], wherein switch sequences and probe sequences overlap; column 7, lines 47-55) and permitting complementary regions to self hybridize to form a second loop (e.g., ribozyme structure 36 of Figure 13) that is detectable (column 14, 34-41) with the added advantage that the assay is quantitative and allows exponential amplification (column 6, lines 1-5).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the detector as taught by Lee et al with the probes that convert from one stem-loop to another as taught by Lizardi et al with a reasonable expectation of success. The

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ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a quantitative assay that allows exponential amplification as explicitly taught by Lizardi et al (column 6, lines 1-5).

Regarding claim 46, the detector of claim 45 is discussed above. Lee et al also teach means for detecting electron transduction between the electrode and the redox moiety when the hairpin (e.g., the hybridization results in a change in the redox properties of a pair of labels that are recorded electrochemically; page 12, lines 5-9).

Regarding claim 47, the detector of claim 46 is discussed above. Lee et al also teach means for inducing electron transduction between the electrode and the redox moiety when the hairpin is formed (e.g., application of an electrochemical potential is applied to induce hybridization; page 17, lines 19-32).

Regarding claim 48 the detector of claim 47 is discussed above. Lee et al also teach the first region is at one end of the probe (e.g., one end is immobilized to the electrode; page 4, line 35-page 14, line 2).

Regarding claim 49, the detector of claim 47 is discussed above. Lizardi et al also teach the third region is at the second end (e.g., Figure 12).

Regarding claim 50, the detector of claim 45 is discussed above. Lee et al also teach the electrode comprises a metal (page 8, lines 15-21).

8. Claims 43 and 51-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al (PCT Publication No. WO 01/40511 A2, published 7 June 2001) and Lizardi et al (U.S. Patent No. 5,312,728, issued 17 May 1994) as applied to claims 42 and 50 above, and further in view of Hashimoto (U.S. Patent Application Publication No. US 2001/0024788 A1, issued 27 September 2001).

Regarding claims 43 and 51, the detector of claims 42 and 50 are discussed above. While Lee et al also teach the electrode comprises a metal (page 8, lines 15-21), Lee et al and Lizardi et al are silent with respect to gold.

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However, Hashimoto teaches a nucleic acid carrier for electric detection of nucleic acids (Abstract) comprising gold electrodes and immobilized thiolated nucleic acids with the added advantage that gold is preferable for immobilizing sulfur-bearing nucleic acids because of the high affinity of gold for sulfur (paragraph 0032).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the detector as taught by Lee et al and Lizardi et al with the gold electrodes as taught by Hashimoto with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in high affinity immobilization of nucleic acids to the electrodes as explicitly taught by Hashimoto (paragraph 0032).

Regarding claim 52, the detector of claim 51 is discussed above. Lee et al also teach the redox moiety is ethidium bromide (page 15, lines 5-15).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

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1. Claims 1-52 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of copending Application No. 11/193,318 in view of Lizardi et al (U.S. Patent No. 5,312,728, issued 17 May 1994). Both sets of claims 1-14 are drawn to electrodes capable of sensing redox moieties, oligonucleotide probes (i.e., aptamers oligonucleotide probes) immobilized on electrodes, first and second positions, internal hybridization, gold electrodes, redox labels, and first, second, and third regions. The claims of the '318 application do not discuss interconversion between hairpins.

However, Lizardi et al teach a probe nucleic acid that is a single molecule (e.g., column 14, Example V and Figure 12) having a first nucleotide sequence complementary to and spaced apart from a second nucleotide sequence with which it self hybridizes to form a first loop (e.g., elements 31-33 of Figure 12, including switch sequences 32 and 33; Example V), wherein upon binding to a target (element 8 of Figure 13), the first sequence binds to the target and the first loop is disrupted (i.e., loop 31 binds to the target [Figure 13], wherein switch sequences and probe sequences overlap; column 7, lines 47-55) and permitting complementary regions to self hybridize to form a second loop (e.g., ribozyme structure 36 of Figure 13) that is detectable (column 14, 34-41) with the added advantage that the assay is quantitative and allows exponential amplification (column 6, lines 1-5).

It would therefore have been obvious to a person of ordinary skill in the art at the time the invention was claimed to have modified the detector as taught by Lee et al with the probes that convert from one stem-loop to another as taught by Lizardi et al with a reasonable expectation of success. The ordinary artisan would have been motivated to make such a modification because said modification would have resulted in a quantitative assay that allows exponential amplification as explicitly taught by Lizardi et al (column 6, lines 1-5).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

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2. Claims 1, 3-6, 8-11, 13-17, and 20-52 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-5, 7-8, 12-16, 25, and 28-38 of copending Application No. 10/810,333. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 1, 4-5, 7-8, 12-16, 25, 28-38 of the '333 application describe all of the limitations of the claims of the instant application; e.g., target polynucleotides, electrodes capable of sensing redox moieties, oligonucleotide probes (i.e., polynucleotide probes) immobilized on electrodes, first and second positions, internal hybridization, gold electrodes, redox labels, and first, second, and third regions. For example, instant claim 3 is drawn to a detector comprising an electrode capable of sensing redox events in a redox moiety, and oligonucleotide probe immobilized on the electrode, the probe having a redox moiety, first and second positions of said redox moiety in the presence and absence of hybridization of the probe to a target, and the second position is closer to the electrode than the first position. These limitations are met by claim 3 of the '333 application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowed.

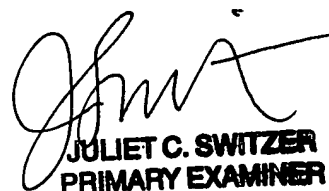
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert T. Crow whose telephone number is (571) 272-1113. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert T. Crow
Examiner
Art Unit 1634



JULIET C. SWITZER
PRIMARY EXAMINER
8/16/06